Epilepsy Research 132 (2017) 91–99

Contents lists available at www.sciencedirect.com

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Long-term clinical outcomes and economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy

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ARTICLE INFO

Article history:
Received 12 October 2016
Received in revised form 14 February 2017
Accepted 12 March 2017
Available online 21 March 2017

Keywords:
Epilepsy
Intractable epilepsy
Economic evaluations
Ketogenic diet
Children
Adolescents

ABSTRACT

Objective: To examine long-term retention rate, clinical outcomes, cost-utility and cost-effectiveness of the Ketogenic Diet (KD) compared with care as usual (CAU) in children and adolescents with intractable epilepsy from a societal perspective.
Methods: Participants were randomized into a KD or CAU group. Seizure frequency, quality adjusted life years (QALYs), side-effects, seizure severity, health care costs, production losses, patient and family costs were assessed at baseline and during 16-months of follow-up. Incremental cost-effectiveness ratios (ICERs) (i.e. cost per QALY and cost per responder) and cost-effectiveness acceptability curves are presented.
Results: 48 children were included in the analyses of this study (26 from KD group). In total, 58% of the KD group completed the follow-up of 16 months; 11 dropped-out for various reasons. At 16 months, 35% of the KD participants had a seizure reduction ≥ 50% from baseline, compared with 18% of the CAU participants. Mean costs per patient in the CAU group were €53,367 (extrapolated) compared to €61,019 per patient in the KD group, resulting in an ICER of €46,564 per responder. Cost per QALY rose well above any acceptable ceiling ratio. At 4-months' follow-up, the KD group showed significantly more gastro-intestinal problems compared to the CAU group. At 16 months, the KD group reported fewer problems compared to CAU. Furthermore, 46.2% of the KD group reported a decrease in severity of their worst seizure compared to 32% of the CAU group.
Conclusion: The KD group resulted in more responders and showed greater improvement on seizure severity. Furthermore, the KD did not lead to worsening of side-effects other than gastro-intestinal problems (only at 4 months' follow-up). However, as only a minimal difference in QALYs was found between the KD group and the CAU group, the resulting cost per QALY ratios were inconclusive.

1. Introduction

Epilepsy imposes a substantial burden on individuals and society as a whole (Strzelczyk et al., 2008; World Health Organisation, 2016). In Europe, about 3.4 million people suffer from epilepsy, corresponding to a prevalence of 5 per 1000 inhabitants (Strzelczyk et al., 2008). In The Netherlands, the health care costs of epilepsy in 2011 were € 248 million accounting for 0.3% of the total budget. Kotsopoulos et al. examined ten epilepsy costs studies in different countries and found the proportion of national health care expenditure on epilepsy to be in the range 0.12–1.12% (Kotsopoulos et al., 2001).

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http://dx.doi.org/10.1016/j.eplepsyres.2017.03.002
0920-1211/

Most patients with epilepsy are provided with an anti-epileptic drug (AED) treatment which is effective in about 70% of the treated patients (Buncher and Tsay, 1994). The remaining 30% patients who suffer from drug-resistant or intractable epilepsy are subjected to a wide range of possible treatments such as epilepsy surgery, vagus nerve stimulation, or deep brain stimulation to improve seizure control and hence the patient's quality of life (QoL). These procedures are, however, invasive and not always applicable for all patients with intractable epilepsy. Poorly controlled epilepsy results in frequent hospitalizations and consequently institutionalization in most cases in the Netherlands.

It has been suggested that the ketogenic diet (KD) can be beneficial to patients with intractable epilepsy (Neal et al., 2008). The KD is a high-fat diet with a restriction on carbohydrates that mimics the metabolic state of fasting. Ketone bodies replace glucose and become the main fuel for the brain's energy demands (Hartman et al., 2007). Although the exact anticonvulsant mechanism of KD is unknown, children with drug-resistant epilepsy have been successfully treated with the KD since the 1920s (Bromfield et al., 2006). Moreover, there are many observational studies (Caraballo et al., 2005; Coppola et al., 2002; Freeman et al., 1998; Kang et al., 2005; Kankirawatana et al., 2001; Kossoff et al., 2002; Kossoff et al., 2005; Vining et al., 1998), reviews (Keene, 2006; Lefevre and Aronson, 2000; Levy and Cooper, 2003; Sinha and Kossoff, 2005) and two randomized controlled trials (RCT)(Neal et al., 2008; Sharma et al., 2013) that suggest the beneficial effects of KD on seizure frequency. In addition, a recently published short-term interim analysis regarding the (cost-)effectiveness of the KD demonstrated a significant reduction in seizure frequency (de Kinderen et al., 2016). None of the previous studies has, however, examined the long-term (cost-)effectiveness of the KD (Levy and Cooper, 2003), which is important in order to make allocation or reimbursement decisions in health care, as policymakers often try to find a balance between costs and effects of interventions.

Hence, this study aims to examine long-term clinical outcomes, cost-utility and cost-effectiveness of the KD compared with care as usual (CAU) in children and adolescents with intractable epilepsy from a societal perspective.

2. Material and methods

2.1. Design

This economic evaluation was conducted alongside a randomized controlled trial (Lambrechts et al., 2017). Subjects were randomized to either the ketogenic diet or to usual care. The total follow-up for the KD group was 16 months; the CAU group was followed for 4 months. A detailed description of the design of this study can be found elsewhere (de Kinderen et al., 2011).

Early in 2016, an interim analysis was published regarding the short-term results of this study (de Kinderen et al., 2016). These results were based on the 4-month comparative phase of the study, after which subjects randomized to the KD were followed for an additional 12 months (with outcome assessments every 3 months). The results in this article are based on the total follow-up and compare findings from the KD group (16 months' follow-up) to the CAU group (4 months' follow-up, extrapolated to 16 months). Fig. 1 is a graphical representation of the study. Analyses are based on the intention-to-treat protocol (ITT). This means that all patients initially randomized to either the KD or CAU group are included in the analyses. Study data of patients randomized to the control group were extrapolated to 16 months as it was assumed that they continued to receive care as usual and hence no sudden change in their health status would occur (for more details on extrapolation, see analysis section).

2.2. Population & setting

This study included both children and adolescents with intractable epilepsy who had to meet the inclusion criteria: age between 1 and 18 years, diagnosed with intractable seizures (i.e. patients in whom at least 2 AEDs failed) and not eligible for epilepsy surgery, no fatty acid oxidation disorders or related diseases, no diabetes or hyperinsulinism, no prolonged QT-time syndrome, no hypercholesterolemia or hypertriglyceridemia, no severe liver, kidney or pancreas diseases, no renal tubular acidosis, no severe behavioral disorder, no malnutrition, no treatment with topiramate or acetazolamide and no positive family history of other risk factors for kidney stones or acidosis. Patients were included between July 2010 until August 2014. The study was conducted by the Academic Center of Epileptology Kempenhaeghe and has been approved by the ethics committee of the Academic Medical Center Utrecht, The Netherlands.

2.3. Intervention

Subsequent to the randomization, patients assigned to the KD group were admitted to the tertiary epilepsy center for a 5-day introduction to the KD. A dietician was in charge for both the introduction and consultation with the parents to determine whether the classical diet, the medium-chain triglyceride (MCT) diet, or a mixture of both diets should be introduced. When only tube feeding was given, a liquid form of the classical KD was used. Patients were instructed to continue taking their prescribed AEDs without change. During the 5-day administration of the KD, ketosis was assessed using two approaches: a daily assessment in urine (in case of those toilet-trained), and assessment in the blood by finger puncture on three occasions. The neurologist, pediatrician and epilepsy nurse also visited the children during this period. After the 5 days in the epilepsy center, parents were in charge of the ketosis check by daily assessment in urine or three times a week in blood (by finger puncture). An electrocardiogram was included in the protocol to screen for prolonged QT syndrome, which has been reported to be a possible side-effect of the KD. The progress of the patients was also tracked by weekly telephone meetings between parents and the epilepsy nurse, and between parents and the dietician. After 4 months, the dietician and epilepsy nurse continued to contact the parents (child) by e-mail or phone on a monthly basis. Furthermore, a visit to the neurologist, pediatrician, dietician and epilepsy nurse was scheduled every three months. Changes in AED regime were only allowed if medically necessary. No further protocol care was given. Outcomes were assessed at baseline and 4, 7, 10, 13 and 16 months after the baseline period.

2.4. Care as usual

Patients assigned to the control group (care as usual; CAU) were also instructed to continue taking their AEDs as prescribed and had weekly telephone meetings with the epilepsy nurse. 6 weeks and 4 months after the randomization, patients of the CAU group were seen by a neurologist, pediatrician and epilepsy nurse. Changes in AED regime were only allowed if medically necessary. No further protocol care was given. Outcomes were assessed at baseline and after 4 months. Given the design of the study, children in the CAU group were offered to receive the ketogenic diet with a delay of four months.

2.5. Outcome measures

2.5.1. Seizure frequency

The seizure frequency was tracked by the use of a daily seizure calendar in which the types of seizures were labeled and described